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Quercetin as an Anticancer Agent: Focus on Esophageal Cancer

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A shortened version of the title: *Quercetin and esophageal cancer*

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Abstract

Esophageal cancer (EC) is regarded as the sixth highest contributor to all cancer-related mortality, worldwide. In spite of advances in the treatment of EC, currently used methods remain ineffective. Quercetin, as a dietary anti-oxidant, is a plant flavonol from the flavonoid group of polyphenols, and can be found in numerous vegetables, fruits, and herbs. Quercetin can affect the processes of cancer-related diseases via cell proliferation inhibitory effects, potential apoptosis effects, and anti-oxidant properties. Of the various types of cancer, the use of quercetin has now become prominent in the treatment of EC. In this review, we discuss how quercetin may be an important supplement for the prevention, treatment, and management of EC, owing to its natural origin, and low-cost relative to synthetic cancer drugs. However, most findings cited in the current study are based on *in vitro* and *in vivo* studies, and thus, further human-based research is necessitated.

Keywords: quercetin; esophageal cancer; flavonoid; apoptosis; anti-oxidant

Practical Applications

- In spite of advances in the treatment of esophageal cancer, currently used methods remain ineffective, therefore, an alternative or complementary therapy is required.

- Quercetin, as a dietary anti-oxidant, can affect the processes of cancer-related diseases via cell proliferation inhibitory effects, potential pro-apoptotic functions, and anti-oxidant properties.

- Quercetin may be an important supplement for the prevention, treatment, and management of EC, owing to its natural origin.

- The low cost of quercetin as supplement or dietary intake, relative to synthetic cancer drugs, is an advantage of the compound which should be considered.

1. The epidemiology and pathophysiology of esophageal cancer

Annually, more than 570,000 individuals are diagnosed with Esophageal cancer (EC), globally (Bray et al., 2018). EC is ranked as the sixth highest contributor to cancer-related mortality worldwide, with over 500,000 deaths in 2018 (Bray et al., 2018). EC is classified into two types according to the type of cells that are involved in the cancer pathophysiology; Esophageal Adenocarcinoma (EAC) and Esophageal Squamous Cell Carcinoma (ESCC) (B. Gupta & Kumar, 2017), respectively. The epidemiology of EC is changing; indeed, ESCC was reported to be the most prevalent form of EC in the preceding four decades, whilst, presently, the incidence of EAC is rising rapidly in the United States and extended parts of Europe. Following these changes in the incidence of EC, among white males, EA has become the most prevalent type (H.-Z. Zhang, Jin, & Shen, 2012). Additionally, EAC is predominantly prevalent in Western countries, while ESCC is the prevailing form in the Middle East to the Northern regions of China, colloquially known as the "*esophageal cancer belt*" (Eslick, 2009).

ESSC involves the squamous cells in the middle portion of the esophagus (Chen et al., 2017). Tobacco and alcohol consumption are the main risk factors for the progression of ESCC (Pandeya, Olsen, & Whiteman, 2013). Nitrosamine and aldehyde levels are increased following tobacco use and alcohol consumption, respectively, and are

considered as possible carcinogenic agents related to ESCC (Stoner, Wang, & Chen, 2007). Furthermore, vitamin A, vitamin C, and trace elements deficiency are the major risk factors for the high prevalence of ESCC in "*esophageal cancer belt*" (Jessri, Rashidkhani, Hajizadeh, Jessri, & Gotay, 2011). Whilst in Western regions; Plummer-Vinson Syndrome, hereditary tylosis, radiation history in thoracic parts, achalasia, weak oral hygiene, and poor economic status are the most prominent risk factors of ESCC (Dar et al., 2013).

EAC affects the gastro-esophageal junction (GEJ) in the lower portion of the esophagus (Alexandre, Long, & Beales, 2014). Dysplasia, the abnormal growth of cells, occurs in the cells with the mucus production responsibility in the GEJ and consequently, EAC occurs in this region (Alexandre et al., 2014). The Gastro-esophageal junction adenocarcinoma is divided into three types, based on the distance of malignancies from the GEJ. Type I (tumors of the distal esophagus), type II (true cardiacarcinoma), and type III (subcardial gastric carcinoma) (Siewert & Stein, 1998). Barrett's esophagus, tobacco smoking, inadequate consumption of fruits and vegetables, obesity (specially, central obesity), and subsequent gastro-esophageal reflux disease (GERD), are the potential risk factors for EAC (Veugelers, Porter, Guernsey, & Casson, 2006). Barrett's esophagus is characterized by the switch between normal stratified squamous mucosa and glandular mucosa in the lining layer of lower esophagus (Fitzgerald, 2005); whilst chronic exposure of the epithelium to GERD is the main cause of Barrett's esophagus induction (Malfertheiner & Hallerbäck, 2005). The incidence of GERD is increasing worldwide (Bevilacqua et al., 2018); moreover, one of the most prominent factors that has a significant effect on GERD causality, is obesity (El-Serag, 2008). Obesity can cause

intra-abdominal pressure on the stomach and, as a result, reflux. (Chang & Friedenberg, 2014). In fact, a higher prevalence of obesity in Europe and US is asserted to have caused higher incidence of GERD and Barrett's esophagus, and consequently, the prevalence of EAC has increased in these regions (Kubo & Corley, 2006). Previous studies have suggested that a history of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the risk of EAC (Khalaf, Nguyen, Ramsey, & El–Serag, 2014). In addition, previous infections with *Helicobacter pylori* in patients is associated with lower risk for the development of EAC (Anderson et al., 2008). Accordingly, lower acidity and reduced secretion of stomach are the possible mechanisms, following *H.pylori* infections, for reducing GERD and EAC risk (Franceschi, Gasbarrini, Polyzos, & Kountouras, 2015). Moreover, it is conceivable that, due to health developments in Western populations, and lower prevalence of *H.pylori* infection, the incidence of EAC is increasing (Blaser, 2008).

2. Latest and current management principles of EC:

2.1. Endoscopic treatment

Due to limited lymph node metastases, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the two most used treatment methods for early stage esophageal cancer (EEC) (Fujishiro, 2008). However, tumor characteristics, nodal (N) and metastatic (M) status, referred to as (TNM) staging, must be evaluated before endoscopic therapy (Pennathur, Gibson, Jobe, & Luketich, 2013). Endoscopic therapy is regarded the best method for patients with severe comorbidities or who do not wish to be a candidate for esophagectomy in muscularis mucosa (MM) or slightly submucosal invasive cancer (Isomoto, Yamaguchi, Minami, & Nakao, 2013). However,

there are several complications related to EMR and ESD, including; pain, bleeding, and perforation, which may be caused by the application of ESD (Isomoto et al., 2013).

2.2. Surgical methods

Open esophagectomy (OE): Surgical resection can be used as a specific treatment method. However, numerous empirical investigations have suggested that it may be better to use resection in combination with other methods, in a multimodal approach (Pennathur & Luketich, 2008). Surgical procedures, such as transhiatal esophagectomy (Kutup et al., 2014), Ivor Lewis esophagectomy (Xie et al., 2014), and three-incision modified McKeown esophagectomy (laparotomy, right thoracotomy and neck anastomosis), (J. Zhou et al., 2009) are examples of currently performed procedures. The use of each method depends on surgical preference and tumor volume; but the application of each approach must result in the complete removal of the tumor with dissection of impacted lymph nodes. Despite all of the advances in esophageal resection techniques, complications such as anastomotic leaks, fistula, postoperative pulmonary complications, and chylothorax can occur perioperatively (Grimminger et al., 2018).

Minimally invasive esophagectomy (MIE): OE is associated with severe morbidity and mortality (Jamieson et al., 2004; Morita et al., 2008). Thus, to remedy such high mortality rates, a new surgical procedure was described in the 1990s (Hoppo, Jobe, & Hunter, 2011; Yamamoto, Weber, Karl, & Meredith, 2013). In this procedure, thoracoscopic mobilization is used to avoid thoracotomy and laparotomy, and consequently, postoperative outcomes such as pulmonary infections are reduced (Palanivelu et al., 2006). There are several approaches for MIE, such as total MIE (laparoscopic and

thoracoscopic esophagectomy) (Watanabe, Baba, Nagai, & Baba, 2013) and hybrid MIE (thoracoscopy and laparotomy/laparoscopy and thoracotomy) (Mariette et al., 2019) which are intricate operations. However, the beneficial effects of MIE in treatment of EC is regarded as controversial (D'Journo & Thomas, 2014; Dhamija et al., 2013; Sarkaria & Rizk, 2014). Indeed, surgical treatments are invasive methods which are not preferred in all patients with cancer, primarily due to the limitation of surgical methods for metastatic lymph nodes (Collins et al., 2011).

2.3. Non-surgical methods

Neoadjuvant chemotherapy: is defined as the administration of complementary agents in EC patients, before the resection of the tumor (Y. Zhang et al., 2018). This procedure has a significant role in the improvement of operability, by shrinking the volume of tumor prior to surgery (Y. Zhang et al., 2018); moreover, radiological investigations can be incorporated for assessing pharmacological effects prior to the operation (Park et al., 2016). However, previous history of cardiovascular diseases (CAD) and kidney disorders for systemic chemotherapy are regarded as contraindications (Huang et al., 2017). Interestingly, the most common procedure for the treatment of locally advanced esophageal carcinoma, tends to vary by country, for instance, Neoadjuvant chemoradiotherapy is regarded as the preferential treatment in the USA (van der Wilk et al., 2018).

Definitive chemo-radiotherapy (CRT): Medicines commonly used in chemotherapy are 5-Fluorouracil, Oxaliplatin, Epirubicin, Docetaxel, and Cisplatin (Al-Batran et al., 2017; Nishida et al., 2019; Sakai et al., 2019). For ESSC localized in the upper third of

esophagus, is regarded as an optimal treatment method, whilst for localized ESSC in the middle or lower esophagus, CRT plus surgery may be the most beneficial procedure (Allum et al., 2011).

Chemotherapy has numerous complications, such as immunosuppression and myelosuppression, reduction of the hematocrit (thrombocytopenia, and anemia), lethargy, renal toxicity, nausea and vomiting, hair loss, secondary neoplasm, infertility, peripheral neuropathy, and cognitive disorders (Ades, Tryfonidis, & Zardavas, 2017; Pearce et al., 2017; Ramirez et al., 2009). Moreover, radiotherapy also has many adverse effects, for example, nausea and vomiting, injury of epithelial surfaces, gastrointestinal sores, inflammation, fibrosis, dryness, polyneuropathy, and lymphedema(Agarwal, Upadhyay, & Agarwal, 2012).

Overall, the selection of the most efficient treatment method is dependent on the involved area, progression level of cancer, and the stage of the disease, whilst the clinical condition of the patients can also affect the selection of treatment method (Agarwal et al., 2012; Cappelli, Shah, & Bingham, 2017; Collins et al., 2011; Newhauser, de Gonzalez, Schulte, & Lee, 2016; Pearce et al., 2017). Currently, despite advances in the treatment of EC, because of the numerous side effects and high cost attributed to novel procedures, current and pervasive methods remain ineffective. Thus, finding new procedures, alternative treatments, and complementary therapies is vital for individuals with EC, and especially in patients with EAC.

3. Quercetin: a potential agent in cancer management

Presently, the use of natural products and medicinal herbs in the treatment and management of health concerns has increased globally, particularly due to the minimal adverse effects, and significant therapeutic impacts these plants are reported to elicit. Previous studies have suggested that natural products can be used instead of, or concomitant to, present pharmacological treatments well, however, the efficacy of these alternative treatments should be evaluated (Firenzuoli, Gori, Crupi, & Neri, 2004; McCulloch et al., 2011). Numerous studies have shown that different medicinal herbs, such as *Cinnamomum* species, *Curcuma* species, *Artemisia* species, and their components, have a wide range of anticancer activities, such as apoptosis induction, angiogenesis inhibition, and cell growth inhibition (Bevara et al., 2018; Jung et al., 2018; Mayzlish-Gati et al., 2018; P. Zhou et al., 2019). These properties in the prevention of cancer development are related to the presence of various ingredients in vegetables, fruits, and medicinal herbs (R. K. Gupta, Soni, Shrivastava, Rajput, & Parashar, 2018). Flavonoids are polyphenolic phytochemicals found abundantly in different types of vegetables and fruits (Mazza, 2018). Flavonoids include; flavonols, flavones, flavanones, flavanols, anthocyanidins, and isoflavones, whilst the structural differences that exist in flavonoid molecules make their bioavailability exclusive (Cassidy et al., 2010; Ding et al., 2016; Gu et al., 2004). In different studies, numerous beneficial properties in flavonoid compounds have been reported, where consumption of these compounds purportedly reduces the risk of cancer, and chronic brain and heart disorders (Kozlowska & Szostak-Wegierek, 2014; Panche, Diwan, & Chandra, 2016).

Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) is a flavonoid compound present in many fruits, vegetables, seeds, and medicinal plants, such as green tea (Iwashina, 2000;

Schröder et al., 2019). Rich sources of quercetin include onions, apples, grapes, berries, broccoli, citrus fruits, tea, and capers (Bischoff, 2008; D'Andrea, 2015). All flavonoids (like quercetin) have a flavone nucleus that consists of two benzene rings linked together with a heterocyclic pyrone ring (T.-y. Wang, Li, & Bi, 2018). Aglycon and glycoside are two prevalent forms of quercetin that play critical roles in the metabolism of this compound (Erlund et al., 2000; Sahpazidou et al., 2014). Indeed, pprevious investigations have demonstrated that the biosynthesis of quercetin and other flavonoids is associated with defensive responses from the plants against environmental agents, including ultraviolet sunlight and lipid peroxidation (Mariani et al., 2008). Quercetin is insoluble in water and slightly soluble in alcohol (Li et al., 2009). The absorption of quercetin glycosides in the small intestine is relatively low, hence, the microflora in lower bowel hydrolyze the quercetin glycosides to quercetin and sugar, and this quercetin will be absorbed into the enterohepatic system (Buchweitz, Kroon, Rich, & Wilde, 2016). The antioxidant functions of quercetin confer beneficial impacts within the body, for instance, inhibitory properties of antioxidant compounds can reduce reactive oxygen species (ROS) (M. Zhang et al., 2011). Due to the high reactivity and instability of ROS, when in high abundance, this agent can cause various chronic disorders in different parts of the human body, including the endocrine system and cancer disturbance (Pham-Huy, He, & Pham-Huy, 2008). Given that quercetin contains high antioxidant capacity, it has been asserted that it may have a role in the prevention of cancers (Khansari, Shakiba, & Mahmoudi, 2009). The effects of quercetin on numerous types of cancers has been related to its capability in decreasing cancer cell growth, inhibition of angiogenesis, ROS

induction in cancerous cells, and apoptosis induction (Igura, Ohta, Kuroda, & Kaji, 2001; Long et al., 2013).

4. Molecular mechanisms uunderlying quercetin-mediated effects in cancer

4.1. Effects on apoptosis induction

Quercetin has a crucial role in the regulation and induction of apoptosis in cancer cells *in vitro* and *in vivo*, and has pro-apoptotic activity through the upregulation of the p53 gene and suppression of Bcl-2 protein. Moreover, following inhibition of transcription of Bcl-2, the apoptosis process occurs in the cell and may inhibit the progression of tumors . In a study performed by Chien et al., increases in p53 expression levels, and mitochondrial and caspase-3-dependent pathways activation was observed in human breast cancer MDA-MB-231 cells, and consequently, apoptotic cell death occurred within cancer cells (Chien et al., 2009). In another study, upregulation of the expression of Bax and cytochrome c (Cyt-c) led to independent mitochondrial apoptosis in human gastric cancer cells (Shen et al., 2016). Indeed, a number of studies have demonstrated that quercetin may play a critical role in apoptosis process through expression of the p53 gene (Chan, Yang, Huang, Liao, & Yeh, 2013; G. T. Kim, Lee, Kim, & Kim, 2014; G. Wang, Zhang, Liu, Sharma, & Dong, 2012). Blueberry is regarded as one of the most abundant sources of quercetin and other flavonoids, such as kaempferol and gentisic acid (Shi, Loftus, McAinch, & Su, 2017). Sezar and colleagues evaluated the anti-cancer effects of different flavonoids extracted from blueberries in HCT-116 colon cancer cell line (Demirel Sezer et al., 2019); reporting that the inhibitors of apoptosis protein (IAPs) were

inhibited at the end of study (Demirel Sezer et al., 2019). IAPs are a group of proteins reported to play a crucial role in the progression of different cancer types, especially in colorectal cancer (Miura et al., 2011).

4.2. Effects on cell growth and proliferation

Inhibition of the cell growth and proliferation may represent a further, distinct, mechanism capable of playing a critical role in the anti-cancer effects of quercetin. Sahpazidou and colleagues investigated the effects of green tea and its components, such as quercetin, on MCF-7 and MDA-MB-231 breast carcinoma cell line, and reported that quercetin decreased the cell proliferation of cancer cells (Sahpazidou et al., 2014). In A375 malignant melanoma cell lines, quercetin inhibited the cell growth through downregulation of the Wnt/β-catenin signaling pathway (Srivastava & Srivastava, 2019). In another study, quercetin induced cell cycle arrest was found in the G1 phase, and was attributed to the downregulation of Cyclin B1 and cyclin-dependent kinase 1 (CDK1) and essential components of G_2/M cell cycle progression (Jeong, An, Kwon, Rhee, & Lee, 2009). Moreover, quercetin also inhibited cell growth in a dose-dependent manner on A375SM human melanoma cells, although conferred no significant effect on A375P human melanoma cell line. Additionally, *in vivo* treatment with quercetin (50 and 100 mg/kg) significantly reduced tumor volume in comparison with a control group (S.-H. Kim et al., 2019).

4.3. Effects on oxidative stress

Reactive oxygen species accumulation is a biotic factor in the incidence of cancer, whilst inhibiting oxidative stress plays an important role in preventing cancer in normal cells

(Lesjak et al., 2018; Rezaei-Sadabady, Eidi, Zarghami, & Barzegar, 2016). In the human body, Granulosa Cells (GCs) are one of the most sensitive cells to ROS (Rashidi et al., 2019). Indeed, Rashidi et al (Rashidi et al., 2019) demonstrated that Quercetin is capable of upregulating the expressions of the antioxidant response element (ARE) pathway, nuclear factor (erythroid-derived 2)-like 2 (Nrf2) gene and thioredoxin (Trx) system in hydrogen peroxide (H2O2)-treated GCs. In HT29 and HCT15 human colon cancer cell lines, quercetin may be able to induce ROS generation in cancer cells, eventually leading to apoptosis (Priyadarsini & Nagini, 2012); indeed, *in vivo* and *in vitro* work has demonstrated destruction of cancer cells following quercetin introduction (Fonseca-Silva, Inacio, Canto-Cavalheiro, & Almeida-Amaral, 2011; Lee, Hwang, Kwon, Surh, & Park, 2010; H. Zhang et al., 2012). The treatment of MCF-7 cancer cell lines with quercetin, quercetin-3′-sulfate, and quercetin-3-glucuronide, respectively, has been shown to lead to the generation of intracellular ROS in these cells (Wu et al., 2018). High ROS production in the body has been associated with some inflammatory mediators, such as cyclooxygenase 2 (COX-2) (Onodera, Teramura, Takehara, Shigi, & Fukuda, 2015); indeed, in HT29 human colon cancer cells, 40 μM of quercetin significantly upregulated the levels of COX-2 as a ROS mediator (Raja et al., 2017).

5. Quercetin-mediated effects in EC

The anti-cancer effects of quercetin, alone (Q), or as a complementary therapy with butyrate (Q+B), in human esophageal 9706 cancer cells has previously been evaluated, with the authors reporting that treatment by Q, B, or both, downregulated the expression of the DNA Methyltransferase 1 (DNMT1), NF-κBp65, Histone deacetylase 1 (HDAC1), Cyclin D1, and upregulated the expression of caspase-3 and cyclin-dependent kinase

inhibitor 2A ($p16^{INK4\alpha}$) levels in Eca9706 cells compared with control (C). Furthermore, following these alterations, the growth and proliferation of cancer cells was inhibited in Q, B ,and Q+B, in comparison with the C; whilst it was also documented that the concomitant effects of Q+B were stronger than Q or B alone (Zheng, Wang, Yang, & Wu, 2014).

Cancer stem cells (CSCs) are one of the most potent agents in the progression of tumors and metastases (Nassar & Blanpain, 2016). Chemo/radiation therapy resistance of these cells is associated with cancer relapse after treatment (Batlle & Clevers, 2017; Nishikawa et al., 2013). CD133 (prominin-1) is a biomarker of CSCs in colorectal cancers (Ren, Sheng, & Du, 2013). The effects of nanoliposomal quercetin (nLQ) alone, and liposomal quercetin (LQ) in combination with CD133 anti-serum, was investigated in human ESCC and Eca-109/9706 cancer stem cells (CSCs) (Zheng, Mo, Li, & Wu, 2014). Accordingly, treatment with nLQ decreased the levels of NF-κBp65, HDAC1, and cyclin D1, and increased the expression of caspase-3. Consequently, apoptosis occurred in the Eca109/9706 cells and the cell growth was inhibited; however, in the combination group, the apoptotic effects were greater than nLQ alone, suggesting that quercetin, as a complementary therapy, is more potent than a specific treatment method (Zheng, Mo, et al., 2014).

The potential anti-cancer effects of flavonols has always been regarded as controversial. Indeed, flavonols (quercetin, kaempferol, myricetin) and flavones (luteolin, apigenin, chrysin) were shown to elicit cell cycle arrest in the G_2/M phase following the upregulation of p21 and downregulation of cyclin B1 in human esophageal squamous cell carcinoma cell line KYSE-510. Furthermore, increases in the levels of PIG3 and cleavage

of caspase-9 and caspase-3 resulted in apoptosis in cancer cells; however, thee effects quercetin and luteolin was greater than other phytochemicals used (Q. Zhang, Zhao, & Wang, 2009). Similarly, Zhang and colleagues demonstrated that the use of quercetin, and other flavonols (quercetin, kaempferol, myricetin) and flavones (luteolin, apigenin, chrysin), has an apoptotic effect on the upregulation of PIG3 and cleavage of caspase-3, -9, and a cell growth inhibitory effect, via up-regulation of GADD45b and 14-3-3σ, and down-regulation of cyclin B1 in a human esophageal adenocarcinoma cell line (OE33) (Q. Zhang, Zhao, & Wang, 2008). Furthermore, Zhang et al reported the cytotoxicity effects of quercetin were more powerful than other components, and that treatment of cancer cells by quercetin, increased the expression of p18 as a cyclin-dependent kinase inhibitor that plays a critical role in the inhibition of cell growth via inducing cell cycle arrest (Q. Zhang, Zhao, & Wang, 2008).

5-fluorouracil (5-FU) is commonly used in the chemotherapy of EC; although, because of the low efficacy of 5-FU, it is administrated in combination with other medicines (Shim et al., 2010). However, chemotherapy activates the Nuclear factor- kappaβ (NF-κB) pathway that inhibits the anti-cancer effects of drugs used to treat EC due to its anti-apoptotic and metastatic effects (Cusack et al., 2001; Voboril et al., 2004; C.-Y. Wang, Mayo, & Baldwin, 1996). Therefore, the use of some herbal adjuvants is suggested to increase the efficacy of chemotherapy in the treatment of EC, and attenuating possible chemoresistance. Chuang-xin et al. investigated the effects of quercetin, 5-FU, and a combination of these two components, on the EC9706 and Eca109 cell lines. Accordingly, the treatment of cancer cells with quercetin, 5-FU, and a combination of quercetin and 5-FU, caused apoptosis in cells; however, in the combination treatment,

because of the inhibitory effects of quercetin on NF-κB activation pathway, the apoptotic effects on cancer cells was greater than two other treatments (Chuang-Xin, Wen-Yu, Yao, Xiao-Yan, & Yun, 2012).

The epidermal growth factor receptor (EGFR) activates downstream pathways such as phosphoinositide3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and ERKs; these two pathways are regarded as critical in the initiation and progression of tumors (Samatar & Poulikakos, 2014). Quercetin-3-methyl ether (Q3ME) is one of the analogs of quercetin, and can inhibit the activation of AKT and ERKs. Moreover, activating protein-1 (AP-1) may be suppressed as a result of treatment by Q3ME in esophageal preneoplastic lesions, and can suppress cell growth and inflammation levels, *in vivo* (Zhao et al., 2018).

6. Conclusion

The incidence of EC is increasing worldwide; however, this type of cancer is still associated with high mortality and morbidity, which may be due to a lack of optimally effective treatments. Presently, natural products are utilized for the treatment or management of numerous disorders, because these plants confer minimal adverse side effects and have a high treatment potential. Quercetin is a flavonoid found in a number of vegetables, fruits ,and herbs, such as green tea, and may be useful alone or in combination with other methods for the treatment of EC. Quercetin has numerous anti-esophageal cancer activities; however,, the pro-apoptotic activities of quercetin in the management of EC is not yet fully understood. In the present review, it was evident that quercetin appears to have greater effects when utilized concomitant to other treatment

methods In this review, we discussed how quercetin may be an efficacious supplement for the prevention, treatment, and management of EC, owing to its natural origin and low cost, relative to synthetic cancer drugs. However, the evidence discussed in the current study is based on *in vitro* and *in vivo* experiments, and there exists little evidence regarding the impact of quercetin on human EC, and, thus, this represents a pragmatic avenue for further research.

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